

# From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: RICHARD R. MYBECK 8010 EAST MORGAN TRAIL SUITE 10 SCOTTSDALE, AZ 85258

## **PCT**

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (day/month/year)

22 JUN 2000

Applicant's or agent's file reference

5367-PCT

PCT/US99/00475

IMPORTANT NOTIFICATION

International application No.

09 JANUARY 1999

Priority Date (day/month/year)

09 JANUARY 1998

Applicant

ARIZONA BOARD OF REGENTS

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

International filing date (day/month/year)

- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks
Form PCT (Washington 2015) 1230 \*

Authorized officer

SREENI PADMAN



## PATENT COOPERATION TREATY

# **PCT**

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 5367-PCT	FOR FURTHER ACTION		ication of Transmittal of International Examination Report (Form PCT/IPEA/416)
International application No.	International filing date (day/mo	nth/year)	Priority date (day/month/year)
PCT/US99/00475	09 JANUARY 1999		09 JANUARY 1998
International Patent Classification (IPC Please See Supplemental Sheet.	or national classification and IPC	;	
Applicant ARIZONA BOARD OF REGENTS			
Examining Authority and is  2. This REPORT consists of a  This report is also according been amended and are to see Rule 70.16 and See	s transmitted to the applicant act total of sheets.  sheets.  sheets, i.e., sheets he basis for this report and/or sheetion 607 of the Administrative In	s of the descets containing	cription, claims and/or drawings which have ng rectifications made before this Authority
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II Priority			÷
III Non-establishme	nt of report with regard to nove	elty, invent	ive step or industrial applicability
IV Lack of unity of	invention		
	ent under Article 35(2) with regar anations supporting such statemen		y, inventive step or industrial applicability:
VI Certain documents	cited		
VII Certain defects in	the international application		
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ate of submission of the demand	Date of	f completion	of this report
09 AUGUST 1999	24 .	APRIL 2000	
lame and mailing address of the IPEA		zed officer	MILIANIS
Commissioner of Patents and Trader Box PCT (209) (305,3232et) (Jul		EENI PAID	MANAGER CHILLS



International	application	No
IIIWI HAUVIIAI	аррисацоп	146

I. I	Basis	f th	rep	rt													
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omRA	ZEHBE	BALLAS	R(Bd	ick) Käutybk 80	amis/	hed to the re	ceivin	g Office	e in res	ponse t	o an in	vitation `	under .	Article	14 are 1	referred	to



International application No.

Novelty (N)  Inventive Step (IS)	Claims Claims		YE:
Inventive Step (IS)	Claims	4 -	
Inventive Step (IS)		1-5	NO
		1-2 and 4-5	
	Claims	3	NO
Industrial Applicability (IA)		1-5	
	Claims	NONE	NO
citations and explanations (Rule 7 Claims 1-5 lack novelty under PCT Article 2		anticipated by Cushman et al. (US natent	No. 5 430 062)
Cushman discloses phenstatin compounds as columns 19-20). Cushman also teaches the u	nd derivatives o	claimed in the instant invention (see for e	
Claim 3 lacks an inventive step under PCT			nt No. 4,996,237).
Pettit teaches the use of similar compounds, polymerization. Such a teaching renders the Pettit's teachings.			
Claims 1-2 and 4-5 meet the criteria set und	er PCT Article	33(3).	
Claims 1-5 meet the criteria set out under Po		).	
NEW CITATIONS NONE			
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International application No.

PCT/US99/00475

Supplemental B	emental B	3
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(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

### **CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below: IPC(6): A61K 31/09, 31/075, 31/66; C07C 43/215, 217/80 and US Cl.: 514/646, 720, 130, 721; 568/331, 332, 631, 646

### I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed: NONE

Form PCT/IPEA/409 (Supplemental Box) (July 1998)\*

### PATENT COOPERATION TREATY

From	46.	INITE	DNI	ATION	LAL	DII	DEAL	1
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# To: **PCT Assistant Commissioner for Patents NOTIFICATION OF ELECTION** United States Patent and Trademark (PCT Rule 61.2) Office **Box PCT** Washington, D.C.20231 ÉTATS-UNIS D'AMÉRIQUE Date of mailing (day/month/year) in its capacity as elected Office 22 September 1999 (22.09.99) International application No. Applicant's or agent's file reference PCT/US99/00475 5367-PCT International filing date (day/month/year) Priority date (day/month/year) 09 January 1998 (09.01.98) 09 January 1999 (09.01.99) **Applicant** PETTIT, George, R. et al 1. The designated Office is hereby notified of its election made: in the demand filed with the International Preliminary Examining Authority on: 09 August 1999 (09.08.99) in a notice effecting later election filed with the International Bureau on: 2. The election was not made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

Authorized officer The International Bureau of WIPO 34, chemin des Colombettes R. Forax 1211 Geneva 20, Switzerland Telephone No.: (41-22) 338.83.38 Facsimile No.: (41-22) 740.14.35

09/582952

# PATENT COOPERATION TREATY

REC'D	16	MAR 2001
WIFO		PCT

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION		ication of Transmittal of Internati nal
5367-PCT		·	Examination Report (Form PCT/IPEA/416)
International application No.	International filing date (day/n	nonth/year)	Priority date (day/month/year)
PCT/US99/00475	09 JANUARY 1999		09 JANUARY 1998
International Patent Classification (IPC) Please See Supplemental Sheet.	or national classification and IF	·	
Applicant ARIZONA BOARD OF REGENTS			
Examining Authority and is	transmitted to the applicant	been preparacording to	red by this International Preliminary Article 36.
2. This REPORT consists of a	•		
been amended and are the	apanied by ANNEXES, i.e., she the basis for this report and/or sh tion 607 of the Administrative	eets containin	cription, claims and/or drawings which have no rectifications made before this Authority. Inder the PCT).
These annexes consist of a to	otal ofsheets.		
3. This report contains indication	ns relating to the following is	tems:	
I Basis of the repo			
II Priority			
III Non-establishme	nt of report with regard to no	ovelty, inven	tive step or industrial applicability
IV Lack of unity of	invention		
V X Reasoned stateme citations and expla	nt under Article 35(2) with regardanations supporting such staten	gard to novelt nent	y, inventive step or industrial applicability;
VI Certain documents	cited		·
VII Certain defects in	the international application		
VIII Certain observation	ns on the international applicat	ion	
	C		HECTED
		VE	RSION
Date of submission of the demand	Date	e of completio	on of this report
09 AUGUST 1999		24 APRIL 200	
Name and mailing address of the IPEA		norized diffee	11/1/201
Commissioner of Patents and Trade Box PCT	marks	SREENIDA	MANABHAN allen for
Washington, D.C. 20231	Tole	phore No.	(703) 308-1235
Facsimile No. (703) 305-3230		priogram.	(703) 300-1233

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International	application	No.

1. Wi			
	th regard to the	elements of the international application:*	
-		ional application as originally filed	
늗	the descript	tion:	
X	Dages	(See Attached)	, as originally filed
	pages		, filed with the demand
	pages	, filed with the letter of	<del></del>
_	<b>.</b>		
х	the claims:	(See Attached)	as originally filed
	pages	(See Attached) , as amended (together with an	v statement) under Article 19
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	pages ———	, filed with the letter of	
	r-8**		
X	the drawing	gs:	
تنا	pages	(See Attached)	, as originally filed
	pages		, filed with the demand
	pages	, filed with the letter of	
_	] 45	a listing part of the description:	
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		ze of publication of the international application (under Rule 49 3/4	n (under Rule 23.1(b)).
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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT $^{\bullet}$

International application No.

Claims   1-3   NC	state	ement			
Industrial Applicability (IA)  Claims  Claims	N	lovelty (N)	Claims	NONE	YE
Industrial Applicability (IA)  Claims  NONE  NO  Citations and explanations (Rule 70.7)  Claims 1-3 lack novelty under PCT Article 33(2) as being anticipated by Cushman et al. (US patent No. 5,430,062).  Cushman discloses phenstatin compounds and derivatives claimed in the instant invention (see for example compound 27 columns 19-20). Cushman also teaches the use of these compounds as anti-cancer drugs.  Claims 1-3 lack an inventive step under PCT Article 33(3) as being obvious over Pettit et al. (US patent No. 4,996,237).  Pettit teaches the use of similar compounds, combrestatins, for the inhibition of cancer cell growth and tubulin polymerization. Such a teaching renders the applicants teaching of similar phensatin prodrugs an obvious extrapolation of Pettit's teachings.  NEW CITATIONS			Claims	1-3	_ NO
Industrial Applicability (IA)  Claims  Claims	I	eventive Step (IS)	Claims	NONE	YE
Claims NONE  Claims NONE  Claims NONE  Claims 1-3 lack novelty under PCT Article 33(2) as being anticipated by Cushman et al. (US patent No. 5,430,062).  Cushman discloses phenstatin compounds and derivatives claimed in the instant invention (see for example compound 27 columns 19-20). Cushman also teaches the use of these compounds as anti-cancer drugs.  ClaimS 1-3 lack an inventive step under PCT Article 33(3) as being obvious over Pettit et al. (US patent No. 4,996,237).  Pettit teaches the use of similar compounds, combrestatins, for the inhibition of cancer cell growth and tubulin polymerization. Such a teaching renders the applicants teaching of similar phensatin prodrugs an obvious extrapolation of Pettit's teachings.		, ,	Claims	1-3	_ NO
Claims NONE  Citations and explanations (Rule 70.7)  Claims 1-3 lack novelty under PCT Article 33(2) as being anticipated by Cushman et al. (US patent No. 5,430,062).  Cushman discloses phenstatin compounds and derivatives claimed in the instant invention (see for example compound 27 columns 19-20). Cushman also teaches the use of these compounds as anti-cancer drugs.  ClaimS 1-3 lack an inventive step under PCT Article 33(3) as being obvious over Pettit et al. (US patent No. 4,996,237).  Pettit teaches the use of similar compounds, combrestatins, for the inhibition of cancer cell growth and tubulin polymerization. Such a teaching renders the applicants teaching of similar phensatin prodrugs an obvious extrapolation of Pettit's teachings.	I	ndustrial Applicability (IA)	Claims	1-3	YI
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	Pettit t	eaches the use of similar compounds rization. Such a teaching renders the	, combrestatins,	for the inhibition of cancer cell growth and tubulin	
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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/00475

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**CLASSIFICATION:** 

The International Patent Classification (IPC) and/or the National classification are as listed below: IPC(6): A61K 31/09, 31/075, 31/66; C07C 43/215, 217/80 and US Cl.: 514/646, 720, 130, 721; 568/331, 332, 631, 646

#### I. BASIS OF REPORT:

This report has been drawn on the basis of the description, page(s) 1-29, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims, page(s) NONE, as originally filed. page(s) NONE, as amended under Article 19. page(s) NONE, filed with the demand. and additional amendments:

Page 30 filed with the letter of 01 February 2000.

This report has been drawn on the basis of the drawings, page(s) 2-5, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
Page 1 filed with the letter of 02 February 2000.

This report has been drawn on the basis of the sequence listing part of the description: page(s) NONE, as originally filed. pages(s) NONE, filed with the demand. and additional amendments: NONE

### Claims

- 1. The method of inhibiting cancer cell growth and tubulin polymerization in an environment inflicted therewith comprising: introducing into said environment a pharmaceutically acceptable carrier and a small but effective amount of phenstatin prodrug.
- 2. Phenstatin prodrugs and derivatives thereof having the structure:

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wherein when R=H and  $R_1 = OCH_3$ ,  $R_2$  is  $OPO_3NA_2$ ,  $OCOCH_3$ , or  $OCH_3$  and when  $R=R_2$ ,  $R_2$  is  $OCH_3$ ,  $CH_3$ , CI or F and  $R_1$  is H and when  $R_1=R_2$ ,  $R_2$  is  $OCH_3$  or  $OCH_2O$  and R is H.

3. The method of inhibiting human cancer cell growth in a host inflicted therewith comprising administering to said host in pharmaceutically acceptable carrier a small but effective amount of a compound selected from the group consisting of phenstatin, phenstatin prodrug and the derivatives thereof having the structure.

wherein when R=H and  $R_1$  = OCH<sub>3</sub>,  $R_2$  is OPO<sub>3</sub>NA<sub>2</sub>, OCOCH<sub>3</sub>, or OCH<sub>3</sub> and when R=R<sub>2</sub>, R<sub>2</sub> is OCH<sub>3</sub>, CH<sub>3</sub>, Cl or F and R<sub>1</sub> is H and when R<sub>1</sub>=R<sub>2</sub>, R<sub>2</sub> is OCH<sub>3</sub> or OCH<sub>2</sub>O and R is H.



International application No. PCT/US99/00475

	SSIFICATION OF SUBJECT MATTER :A61K 31/09, 31/075, 31/66; C07C 43/215, 217/80		•			
	:514/646, 720, 130, 721; 568/331, 332, 631, 646	national classification and IPC				
According to International Patent Classification (IPC) or to both national classification and IPC  B. FIELDS SEARCHED						
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	ata base consulted during the international search (na	me of data base and, where practicable,	search terms used)			
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C. DOC	UMENTS CONSIDERED TO BE RELEVANT					
Category*	Citation of document, with indication, where ap	propriate, of the relevant passages	Relevant to claim No.			
X	US 5,430,062 A (CUSHMAN et Document.	al) 04 July 1995, Whole	1-5			
Y	US 4,996,237 A (PETTIT et al) Document.	26 February 1991, Whole	1-3			
A	US 5,561,122 A (PETTIT) 01 October	r 1996, Whole Document.	1-5			
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### (54) Title: SYNTHESIS OF PHENSTATIN AND PRODRUGS THEREOF

#### (57) Abstract

A newly discovered antineoplastic compound denominated "phenstatin" is herein described as are synthetic methods for producing phenstatin and the active prodrug thereof. Phenstatin was converted to the sodium phosphate prodrug (3d) by a dibenzylphosphite phosphorylation and subsequent hydrogenolysis sequence  $3b\rightarrow 3c\rightarrow 3d$ . Phenstatin (3b) was found to be a potent inhibitor of tubulin polymerization and the binding of colchicine to tubulin comparable to combretastatin A-4 (1b).